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COX-2 Selective Nonsteroidal Anti-Inflammatory Drugs

Do They Really Offer Any Advantages?

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are responsible for substantial morbidity and mortality as a result of the complications associated with gastroduodenal ulcers, such as perforation and bleeding. The central mechanism leading to the gastroduodenal toxicity of NSAIDs is their ability to inhibit mucosal prostaglandin synthesis. Recent recognition that there are 2 isoforms of the enzyme cyclooxygenase (COX) responsible for prostaglandin synthesis has enabled the development of drugs capable of sparing the gastric mucosa. The inducible COX-2 enzyme is responsible for some aspects of pain and inflammation in arthritis while the constitutive COX-1 enzyme appears responsible for most of the gastro-protective prostaglandin synthesis in the stomach and duodenum. Drugs selective for COX-2 probably act by binding to a pocket in the enzyme that is present in COX-2 but not in COX-1. As a result, drugs that have little or no COX-1 activity across their therapeutic dosage range have been developed. Two drugs that are claimed to be highly selective or specific in their ability to inhibit COX-2, rofecoxib and celecoxib, are now available on prescription in the US and rofecoxib is available in Europe. Short term volunteer studies of 7 days' duration and patient studies of 6 months' duration have shown these drugs to have a level of gastroduodenal injury that is similar or equivalent to that seen with placebo, whereas high rates of damage and ulceration are seen with nonselective NSAIDs. In addition, there appear to have been fewer perforations, clinical ulcers and bleeds in the phase III clinical trials of these agents, compared with nonselective NSAIDS.

However, more experience will be needed before this promise can be confirmed. In addition, COX-2 inhibitors share the adverse effects of NSAIDs outside the gastrointestinal tract that are dependant on COX-2 inhibition.

1. Background

1.1 Cyclooxygenase

The cyclooxygenase (COX) enzyme catalyses the first step in the conversion of arachidonic acid to prostanoids (prostaglandins and thromboxanes). It is now clear that this enzyme exists in at least 2 distinct isoforms; a largely constitutive form termed COX-1 and a largely inducible isoform termed COX-2. The inducible form is expressed primarily in pathophysiological conditions, and is up-regulated by cytokines and growth factors. Induction of this enzyme can lead to increased production of mediators that augment inflammatory conditions. This can be seen in conditions such as rheumatoid arthritis where

increased expression of 'COX' immunoreactivity in synovial tissue parallels the severity of inflammatory response.[1]

1.2 Gastrointestinal Effects of 'Non Selective' NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed groups of drugs worldwide and are highly effective as analgesic, antipyretic and anti-inflammatory agents. Their therapeutic benefits as well as their toxicity are attributable to inhibition of prostaglandin (PG) synthesis. Prostaglandins are important mediators of many physiological processes; they regulate vascular homeostasis, kidney function, ovulation and parturition. Inhibition of cyclooxygenase can therefore potentially have deleterious effects on a wide range of systems. In a significant minority of users gastrointestinal adverse effects result.[2] Most of these are evident in the stomach or duodenum. Long term NSAID ingestion commonly causes gastric erosions[3] and there is a high prevalence (20%) of gastroduodenal ulceration amongst individuals using them long term.[3] NSAID damage is silent in the majority of people, so that complications often occur without warning symptoms. Case control studies suggest a 2- to 5-fold increase in relative risk and a 30% attributable risk of ulcer perforation, upper gastrointestinal bleeding and death for users of NSAIDs.[3] NSAIDs also affect small and large bowel; an 8 to 10% prevalence of small intestinal ulceration has been reported[4] as well as an enhancement of small and large bowel perforation amongst those using NSAIDs long term. Growing evidence associates NSAIDs with relapse of inflammatory bowel disease.[5]

1.3 NSAIDs and Cyclooxygenase

The common basis by which the various NSAIDs achieve their therapeutic effects is through their blockade of prostaglandin synthesis by their inhibition of the cyclooxygenase enzyme.[6] The gastrointestinal adverse effects of these drugs can also be largely attributed to cyclooxygenase inhibition. As a result of this inhibition, NSAIDs abrogate a series of key prostaglandin-dependent mechanisms in the gastrointestinal tract including blood flow, mucus and bicarbonate secretion, and the maintenance of a hydrophobic waxy mucus and cell membrane at the surface of epithelial cells.[7] Because inhibition of prostaglandin synthesis is central to both the beneficial and toxic effects of NSAIDs, they have been regarded as a double-edged sword. The discovery that the cyclooxygenase enzyme exists in 2 isoforms,[8-10] with COX-2 being the primary isoform at sites of inflammation, led to suggestions that inhibition of this isoform accounts for the therapeutic benefits of NSAIDs whereas inhibition of COX-1 results in their shared adverse effects. Based on this hypothesis and fuelled by the huge potential market for these drugs, there have been intense efforts made to develop specific inhibitors of the COX-2 isoform.

2. Selectivity

2.1 Achieving Selectivity

X-ray crystallography of COX-1 and COX-2 has vastly improved our ability to understand how NSAIDs work by demonstrating the 3-dimensional structure of these enzymes and illustrating how alterations in drug structure could influence their ability to inhibit one or other form of cyclooxygenase selectively.[11] Both isoforms are fairly similar, consisting of a long narrow channel with a hairpin bend at the end. In both enzymes, the channel is lipophilic so that when cellular injury leads to the release of precursor arachidonic acid, it is drawn into the channel and the first step of prostaglandin synthesis initiated by the addition of two oxygen molecules and the removal of a free radical.

There are, however, a number of key differences between COX-1 and COX-2. In particular, there is a single amino acid difference between both isoforms at position 120. The replacement of isoleucine at this site in COX-1 by the smaller molecule valine in COX-2 leaves a defect in the inner lining of the enzyme with formation of a small side pocket. An ability to bind within this side pocket appears to be the basis of COX-2 selectivity for many drugs.[12,13]

2.2 Calculating Selectivity

A wide diversity of systems have been developed to calculate relative potency of these drugs against COX-1 and COX-2. These have variously used whole blood, recombinant enzymes and transfected cells.[14,15] Results vary considerably depending on which system is used and there is little agreement on which should be the gold standard. Currently, a whole blood assay in which platelet derived thromboxane during clotting is used to assay COX-1 and PGE_2 stimulated by lipopolysaccharide to assay COX-2 is commonly favoured. However, there are some drawbacks to this assay, particularly with the different time course for assessment of the two enzymes. Recently, a variation on this assay that uses a pre-stimulated macrophage cell line to assay COX-2 has been developed in an attempt to overcome these drawbacks.[15] As the primary aim of determining COX-2 selectivity is to indicate the potential gastrotoxicity of a drug, the best screening test in the future might be a direct measure of effects on gastric and duodenal prostaglandins *in vivo*. However, a consensus has yet to emerge as to how this should be done.

3. Nonselective NSAIDs

In COX-1/COX-2 selectivity assays, most standard NSAIDs are shown to be mixed COX-1/ COX-2 inhibitors and indeed most tend to be more effective against COX-1 than COX-2.[14] This probably undermines attempts to relate their gastrointestinal toxicity to their COX-2 selectivity alone rather than other factors such as potency.

4. Preferential Inhibitors

Some existing NSAIDs have been claimed to be preferential COX-2 inhibitors, at least at low dosages. These include meloxicam, nimesulide and etodolac. Depending on the assay used to characterise concentrations causing 50% inhibition (IC_{50}), these drugs have been quoted as being 1.25 to 1000 times more selective for COX-2 than COX-1.[14-22] In the human whole blood assay, all three drugs are calculated to be less than 20-fold selective for COX-2.[14,16,20-23] According to the COX-2/COX-1 selectivity hypothesis it would be expected that these drugs have less effect on physiological prostaglandin production than nonselective NSAIDs whilst preserving the ability to inhibit the prostaglandin production seen in inflammation. They might thus be expected to have an improved gastrointestinal profile with no loss of efficacy as anti-inflammatory agents.

4.1 Meloxicam

Meloxicam is prescribed for once daily administration with an efficacy range of 7.5 to 22.5 mg/day. The level of gastric injury seen with meloxicam 7.5 mg/day for 23 days in healthy volunteers was similar to placebo.[24] At a higher dosage of 15 mg/day, levels of injury intermediate between that seen for placebo and piroxicam were seen.[24] Meloxicam seems to be a drug that is well tolerated in symptomatic terms. Global analysis of adverse effects in efficacy trials supports this contention.[25]

The potential benefit of meloxicam 7.5 mg/day has also been assessed in two large scale tolerability studies.[26,27] In both studies meloxicam given for 1 month caused significantly fewer gastrointestinal adverse events than its comparators – piroxicam 20 mg/day or diclofenac 100 mg/day. Although there was a suggestion that there might have been fewer hospital admissions with meloxicam than diclofenac, these studies did not investigate the effect of meloxicam on ulceration or ulcer complications in a useful or systematic way. However, it is clear that in clinical practice, patients taking meloxicam can develop ulcer complications.

4.2 Nimesulide

Although nimesulide demonstrates some COX-2 selectivity in *in vitro* assays, the gastrointestinal tolerability of this agent has not proven to be superior to other NSAIDs.[28] Although early endoscopic trials in healthy volunteers suggested a better gastrointestinal adverse events profile for nimesulide, a large epidemiology study from Italy has shown that in clinical practice ulcer complications are as common with nimesulide as with nonselective NSAIDs.[29]

This may be because selectivity for COX-2 is lost when higher dosages, often required for beneficial effects, are employed.

4.3 Etodolac

Etodolac is prescribed twice daily as it has a short half-life. It has been established in clinical studies to be as effective as nonselective NSAIDs in patients with osteoarthritis (OA) or rheumatoid arthritis (RA). In patients with RA, naproxen 1000mg for 4 weeks reduced PGE2 and PGI2 levels in gastric biopsies but etodolac 600mg had no effect on prostaglandin levels (and caused fewer mucosal lesions).[30] It is not clear how sensitive this assay was to minor cyclooxygenase inhibition. When given for 7 days to healthy volunteers, etodolac 600 mg/day resulted in less acute injury to the stomach and duodenum than indomethacin 200 mg/day, naproxen 1000 mg/day or ibuprofen 2400 mg/day.[31] Although these results suggest an improved gastrointestinal adverse effect profile for etodolac, larger scale studies directly addressing tolerability are needed to determine its true clinical value.

5. Specific Inhibitors

Two of the drugs which have been claimed to be a new class, COX-2 specific inhibitors, have received US Food and Drug Administration (FDA) approval.

5.1 Rofecoxib

In recombinant enzyme assays the IC_{50} of rofecoxib for COX-2 was 1.8×10^{-8} mol/L compared with an IC_{50} of 1.5×10^{-5} mol/L for COX-1 (selectivity ratio >800).[32] Selectivities of 36 and 77 have been reported when tested *in vitro* in a whole blood assay.[15,33] When assessed by whole blood assay *ex vivo*, rofecoxib was shown to be COX-1 sparing i.e. it did not affect platelet thromboxane production at doses up to 1 g/day.[33] In the William Harvey modified assay[15] the *in vitro* selectivity of refecoxib was 204. Rofecoxib has no effects on the gastric mucosa *in vivo* when given to healthy volunteers at doses up to 50mg once daily for 5 days.[34,35] Phase II efficacy studies established a dosage range of 12.5 to 25 mg/day for patients with OA.[36] Phase III studies confirmed that efficacy at these dosages is similar to ibuprofen 2400 mg/day or diclofenac 150 mg/day.[36-38] Rofecoxib 50mg was effective as an analgesic in studies of dental pain.[39,40]

The gastrointestinal profile of rofecoxib is very impressive. In healthy volunteers, levels of gastric injury after 7 days were considerably less with rofecoxib 250 mg/day than with ibuprofen 2.4 g/day or aspirin (acetylsalicylic acid) 2.6 g/day, and similar to placebo.[41] Rofecoxib 25 mg/day and 50 mg/day for 7 days resulted in no increase in small bowel permeability, in contrast to indomethacin,[42] and no significant increase in faecal occult bleeding in contrast to ibuprofen 2.4 g/day when taken for one month.[43] In 2 large endoscopic studies, the rate of ulceration in patients receiving rofecoxib 25 or 50 mg/day was compared with placebo over a 12-week period and ibuprofen 2.4 g/day for 24 weeks.[44,45] Across these 2 studies, the rate of ulceration at 12 weeks was 7.3% with placebo, 4.7% with rofecoxib 25 mg/day and 8.1% with rofecoxib 50 mg/day compared with 28.5% with ibuprofen.

Preliminary data on ulcer complications occurring in phase III studies have been published. Of 62 potential events occurring in 2291 patient years, 49 were clinically confirmed perforations, ulcers or bleeds. With rofecoxib, the cumulative incidences of confirmed peptic ulcer bleeds (PUBs) in 1 year was 1.5% versus 2.68% with comparator NSAIDs ($p = 0.006$).[46] A prospective study investigating whether PUBs are reduced is underway.

On the basis of these findings, rofecoxib is licensed in the US, UK and many other countries for long term use in OA and for acute pain.

5.2 Celecoxib

In recombinant enzyme assays celecoxib has been reported to be 375-fold selective for COX-2[47,48] and dosages of 1200 mg/day (50% higher than highest dosage studied in efficacy trials) have no effect on serum thromboxane or platelet function in human whole blood.[49] *In vitro* cell activities in the human whole blood assay of 1.4 and 6.6 have been reported, with a value of 3.133 in the William

Harvey modified assay.[15] In these assays celecoxib selectivity was closer to that of meloxican than that of rofecoxib. However, currently there is some doubt about how selective celecoxib is. In Warner's novel assay, celecoxib was less selective than rofecoxib, and similar to meloxicam in its selectivity.[15] The effects of celecoxib on gastric prostaglandin production have not been published.

Dosage ranges of 100 to 400 mg/day for OA and 200 to 800 mg/day for RA, established in phase II trials,[50] have been confirmed by phase III efficacy trials.[44,51-53] Celcoxib administered at these dosages has been shown to be of similar efficacy to naproxen 1000 mg/day or diclofenac 150 mg/day in the management of the symptoms of OA and RA.

In contrast to rofecoxib, phase III endoscopic data on the incidence of ulcers with celecoxib was gathered from efficacy studies rather than specially designed toxicity studies.[44,51,52,54,55] In all these studies, the rate of ulceration with celecoxib was similar to that found with placebo. All but one of the studies found a substantially lower rate of ulceration with celecoxib than with naproxen or diclofenac. In one study, the rate of ulceration with celecoxib was not significantly different from the (unexpectedly low) rate of ulceration seen with diclofenac.[51,54]

Preliminary data on ulcer complications occurring in phase III studies have been published. Of 101 potential events occurring in 1763 patient years, 11 were considered to be clinically significant, 2 with celecoxib and 9 with the comparator NSAID.[56] A prospective study investigating whether PUBs are reduced is underway.

Celecoxib has shown efficacy in the dental pain model[55,57] but has not yet been licensed by the FDA for this indication.[58]

On the basis of these data, celecoxib is licensed for use in chronic OA and RA in the US.

6. Assessment

COX-2 inhibitors were developed in an effort to circumvent the gastroduodenal toxicity associated with nonselective NSAIDs. The data for both rofecoxib and celecoxib leave little doubt that this has been achieved. Data concerning their effects on ulcer complications are limited but there seem few reasons to doubt that current ongoing outcome studies will show a reduction in such complications compared with nonselective NSAIDs. Nevertheless, there are a number of uncertainties remaining about COX-2 inhibitors. These include:

- *H. pylori*. This prevalent infection induces COX-2 in the stomach.[59,60] However, there is little evidence that it becomes a dominant source of functional prostaglandins[61] or that use of COX-2 inhibitors enhances risks associated with *H. pylori*.[45]
- Ulcer healing injury[61] and ulceration[62,63] induces gastric mucosal COX-2 and retards healing[63] in animal models. Data in humans are not available. It seems likely that this issue will be clarified in the next 2 years.
- Likewise, COX-2 is induced in inflammatory bowel disease.[64-66] This is important since NSAIDs provoke relapse of colitis. Whether this is related to their ability to inhibit COX-1 or COX-2 is currently unclear.
- Like NSAIDs, COX-2 inhibitors appear to cause dyspepsia (FDA hearings and websites), although perhaps to a lesser extent than nonselective NSAID comparators.[51,67] Whether this is due, in part, to oesophagitis, which is known to occur with NSAIDs is not clear.
- Renal effects of NSAIDs. NSAIDs produce renal toxicities by at least 3 mechanisms. COX-1–dependent impairment of renal blood flow and creatinine clearance that can enhance renal failure in compromised individuals, salt and water retention, dependent at least in part upon juxtaglomerular COX-2 expression,[68,69] and a rare ability to induce papillary necrosis. Both rofecoxib and celecoxib have been associated with lower extremity oedema.[51,54,67] Specific COX-2 inhibitors seem to share with nonselective NSAIDs the ability to reduce sodium excretion, at least over the first 72 hours of treatment, but may not share the ability to decrease the glomerular filtration rate which may therefore

be a COX-1–dependent function.[70] More work in this area is needed.

- Aspirin-sensitive asthma. This is associated with COX-2 induction,[71] and COX-2 inhibitors are contraindicated in patients with aspirin-sensitive asthma.
- Cardiovascular effects. Recent demonstrations that COX-2 can be induced in vascular tissue[72] and that COX-2 inhibitors substantially reduce whole body prostacyclin biosynthesis[73] have caused concern that COX-2 inhibitors may provoke vascular disease. If true, this would more than abrogate their gastrointestinal advantages, given the relative background incidence of the two problems. However, there are no suggestions of an increased death rate from vascular disease following the launch of celecoxib and rofecoxib. Moreover, COX-2 is widely expressed in atherosclerotic lesions[74] where, by enhancing inflammatory oedema, resulting prostaglandins could be harmful (and cyclooxygenase inhibition by implication beneficial). It is thus possible that COX-2 inhibition could be harmful, neutral or beneficial to patients with atherosclerotic vascular disease.
- Anti-inflammatory effects of prostaglandins. A recent paper has attracted attention by showing, in some animal models, that COX-2 has anti-inflammatory properties during the late phase of chronic inflammation.[75] This has been known for prostaglandins for at least 20 years and it is relevance to arthritis is not clear.
- Oral tolerance. COX-2 may play an important role in oral tolerance.[76] More work will be needed to know the implications for human use of COX-2 inhibitors.
- The sulfonamide nature of celecoxib is theoretically a disadvantage with regard to adverse effects compared with rofecoxib. However, reports of an increased incidence of Stevens Johnson's syndrome or bone marrow toxicity have not emerged since the launch of celecoxib.

7. Alternatives

7.1 Current Regimens

It is clear that in patients with OA, at least, NSAIDs should be avoided and use of non-opioid paracetamol and opioids considered as first line therapy for pain control. In those in whom NSAID use is necessary, the currently recommended regimen for ulcer prophylaxis is to combine these drugs with a cytoprotective agent, be it proton pump inhibitor (PPI) or prostaglandin analogue.[77] Both approaches have proven effective for this indication. Differences in study design do not allow a comparison between this approach and selective COX-2 inhibitor use. There are some potential concerns with long term acid suppression and with COX-2 inhibitors, and both need to be compared directly in a randomised controlled trial.

7.2 Other NSAIDs

A number of other compounds may also prove to be safer NSAIDS. These include the nitric oxide-releasing–NSAIDs (NO-NSAIDs).[78,79] NO is recognised as an important mediator of gastrointestinal mucosal defence exerting many similar actions to prostaglandins.[78,80,81] NO-NSAIDs have a NO moiety linked to a conventional NSAID which they can in theory donate to gastric mucosa to counterbalance the harmful effects of the parent NSAID.[78] This modification does not interfere with the ability to inhibit cyclooxygenase. They do not appear to retard the healing of established gastric ulcers in animal studies[79] and they maintain the beneficial effects of COX-1 inhibition so they can be prescribed for cardiovascular prophylaxis. However, as yet, these advantages are theoretical as NO-NSAIDs are some way from systematic human study.

8. Wider Prescribing Indications?

It is fortunate that 'safer NSAIDs' are being developed as the indications for NSAID prescribing are widening. There is strong epidemiological evidence supported by laboratory studies that NSAIDs

can halt or slow the development of colon cancer.[82] The onset/progression of Alzheimer's disease has also been shown in epidemiological surveys to be slowed by NSAIDs.[83] COX-2 is up-regulated in both these conditions[82,84] but whether it is by the inhibition of this isoform that NSAIDs mediate these beneficial effects is not known and further investigation is required. This is essential to know before we can postulate whether selective inhibitors will be prove useful for the prophylaxis of these diseases in populations at high risk.

9. Conclusions

Despite their toxicity, NSAIDs represent a sizeable portion of the market of drugs used in the treatment of pain and inflammation. There is no doubt that COX-2 inhibitors have a superior gastrointestinal safety profile than nonselective NSAIDs. COX-2 inhibitors appear to be as effective as nonselective NSAIDs in arthritis, although such comparisons are difficult to draw with precision. As yet there are insufficient data with celecoxib for this drug to be licensed for acute analgesia. The fact that COX-2 is constitutively expressed in the kidney and plays a part in the handling of salt and water means that COX-2 inhibitors are likely to share at least some of the renal adverse effects of nonselective NSAIDs and it is clear that patients taking COX-2 inhibitors can develop fluid retention and ankle oedema. Exactly which renal adverse effects are retained by COX-2 inhibitors and whether these are a class effect are outstanding issues that require further classification.

Further evidence is needed to determine whether the safety of COX-2 inhibitors in all high risk subgroups is the same as in the overall populations in which they have been studied, although preliminary data are encouraging.[45,46,54,85] Because COX-2 inhibitors can cause dyspepsia (albeit at a lower rate that nonselective NSAIDs), drug regimens that use PPI co-protection may have some symptomatic advantages. The current recognition that COX-2 is an important source of prostacyclin is a challenging finding in relation to COX-2 inhibitor use, although no evidence has emerged to suggest that this translates into an increased risk of cardiovascular disease with their use. Nevertheless further evidence and evaluation of these issues will be needed before the initial very favourable data on COX-2 inhibitors can be confirmed as a therapeutic revolution.

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